Neuroscience Module

Lecture (3)

Ammonia metabolism

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Lecture Key points

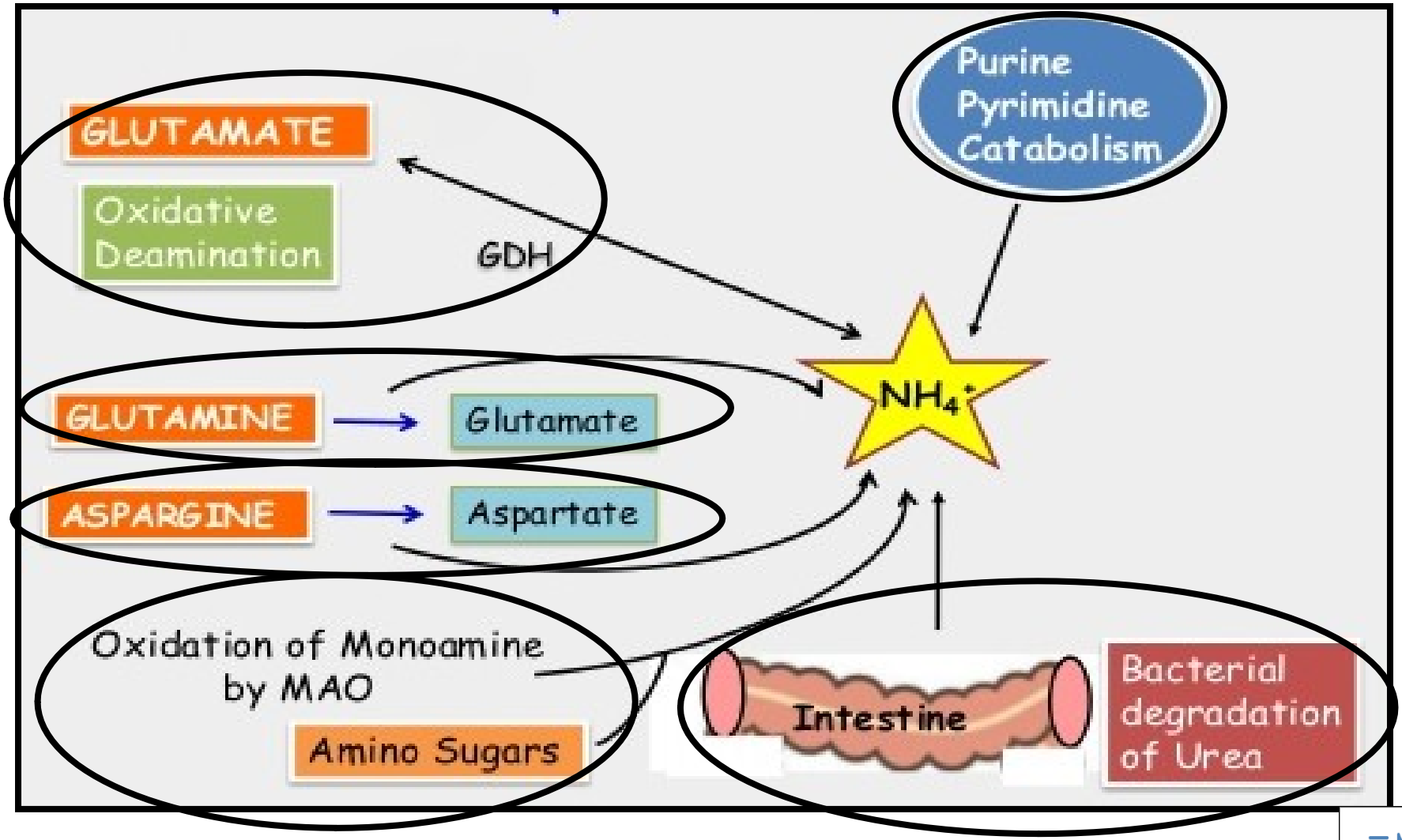
- Ammonia toxicity, transport and detoxification through urea cycle

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Justify the causes of ammonia toxicity
2. Outline the transport of ammonia in the blood
3. Illustrate the reactions of urea cycle

Sources and fate of ammonia



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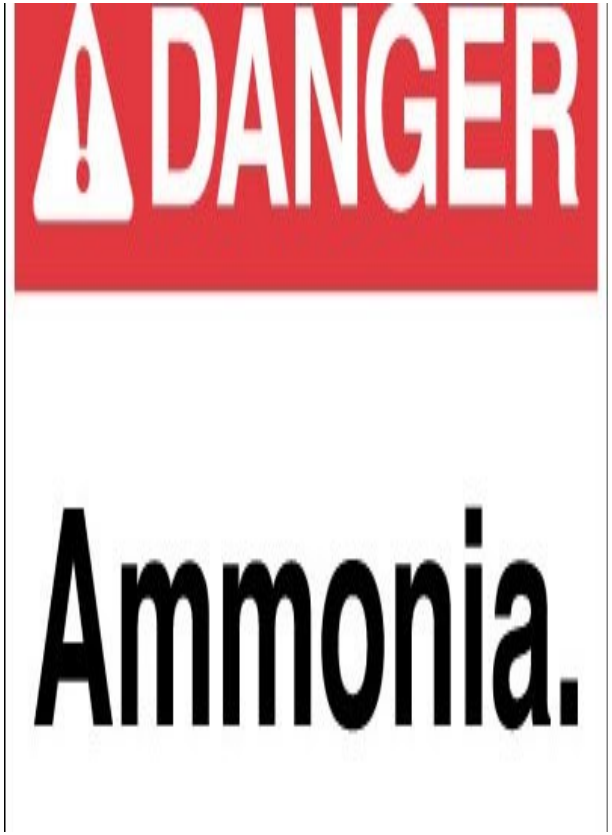
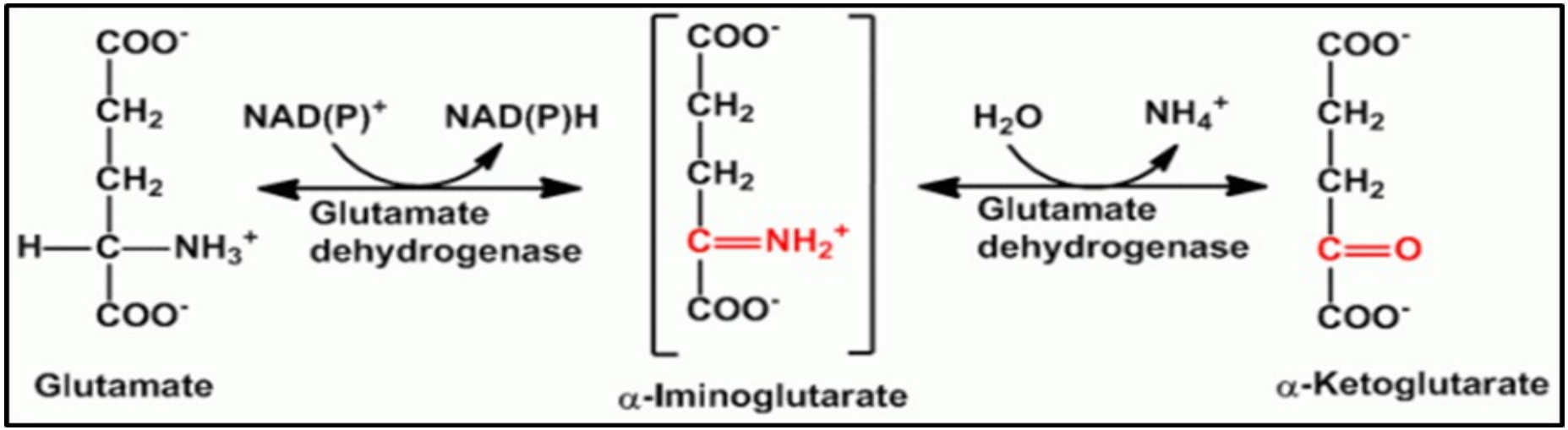
STOP


DANGER
Ammonia.

1) The level of α-KG is reduced



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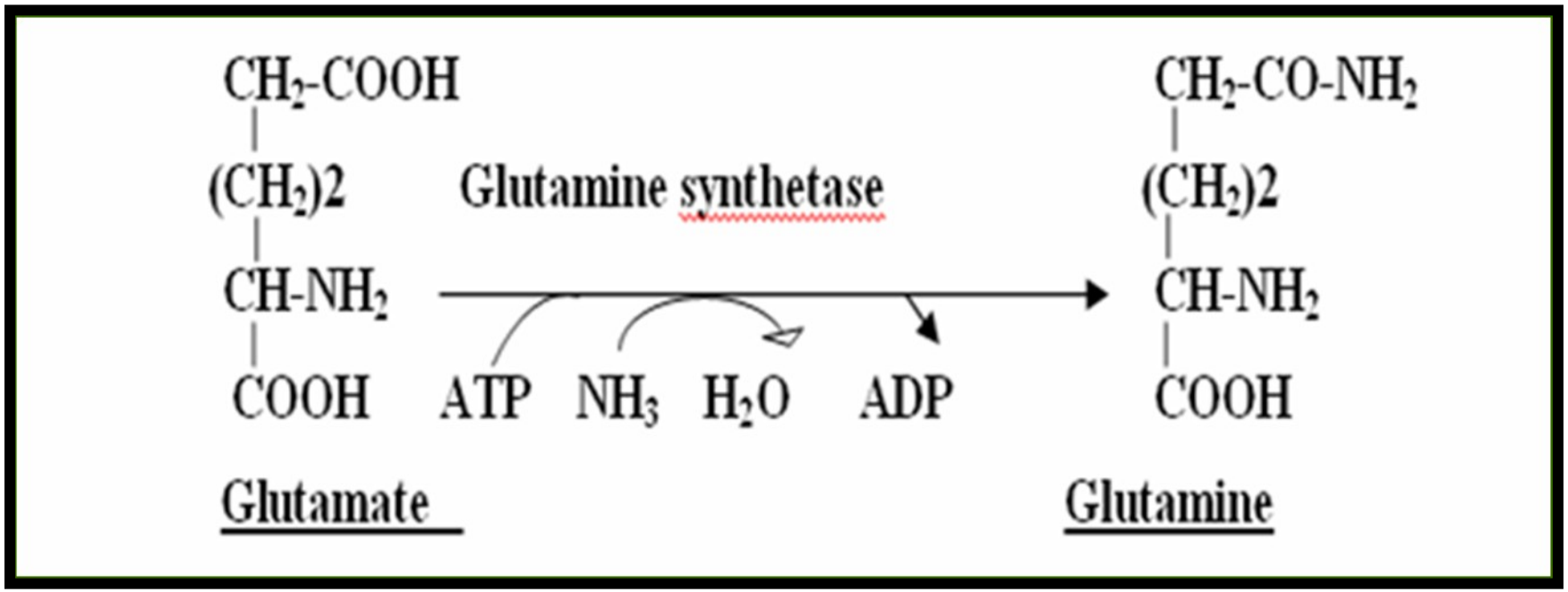
- **shortage in TCA-cycle**
- **and ↓ ATP generation which is**
- **required for various brain activities**

2) Depletion of glutamate in brain (to form glutamine)



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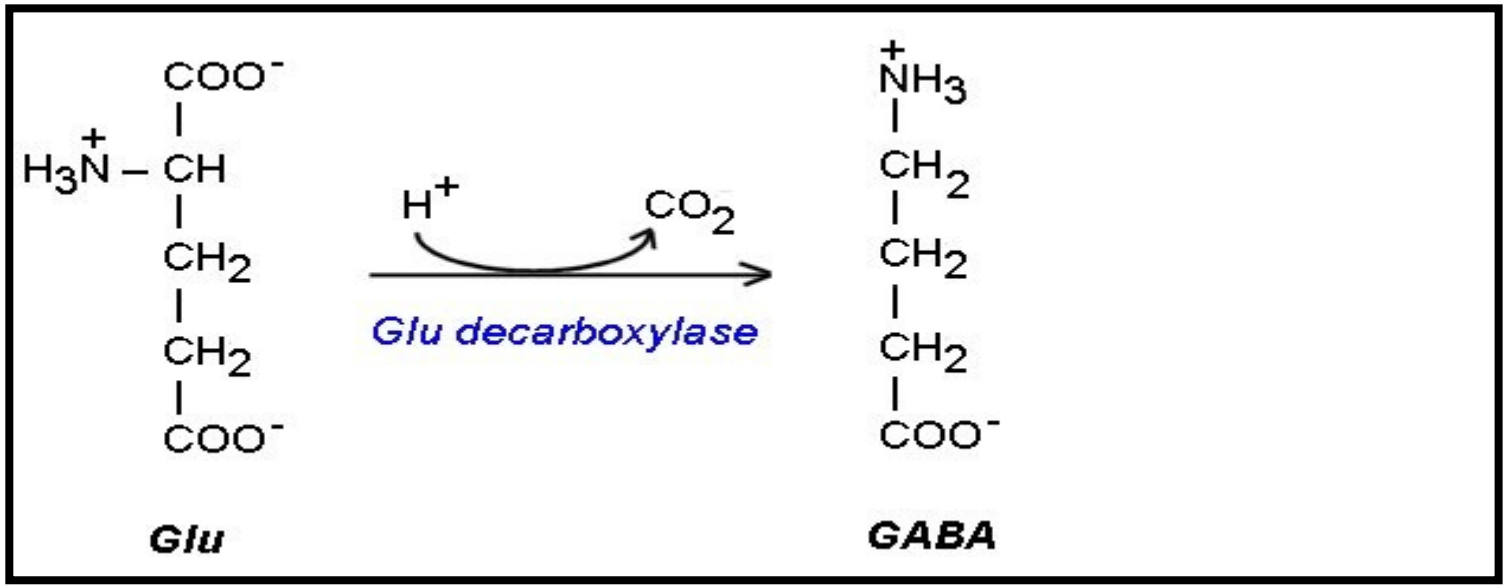
2) Depletion of glutamate in brain decreases production of GABA



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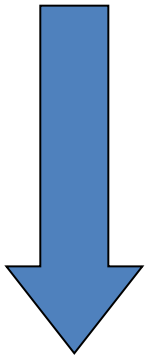
3) Elevated levels increases the permeability to k^+ and Cl^- ions to the brain.



- **Interference with electrical activity of the brain**

4) Glutamine causes osmotic shift of water into cells resulting in cerebral edema.

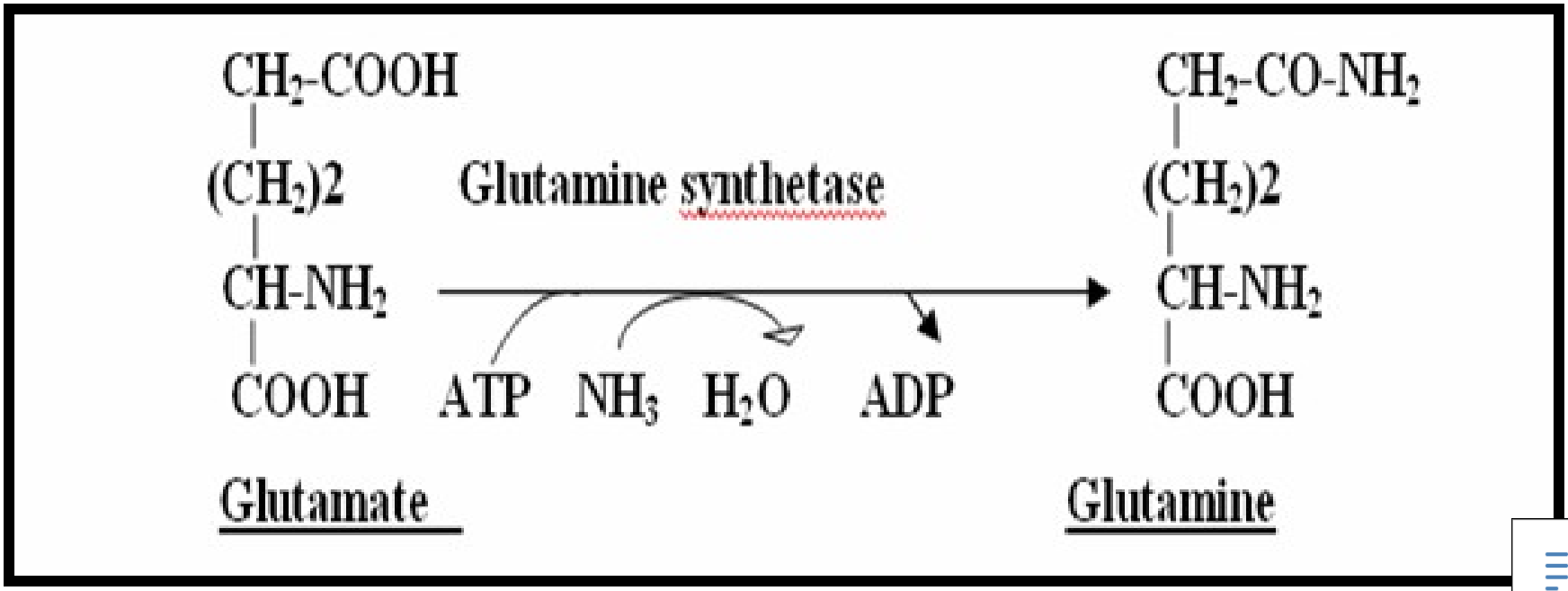
5) Excess glutamine is exchanged with Tryptophan a precursor for serotonin (Excitatory neurotransmitter).

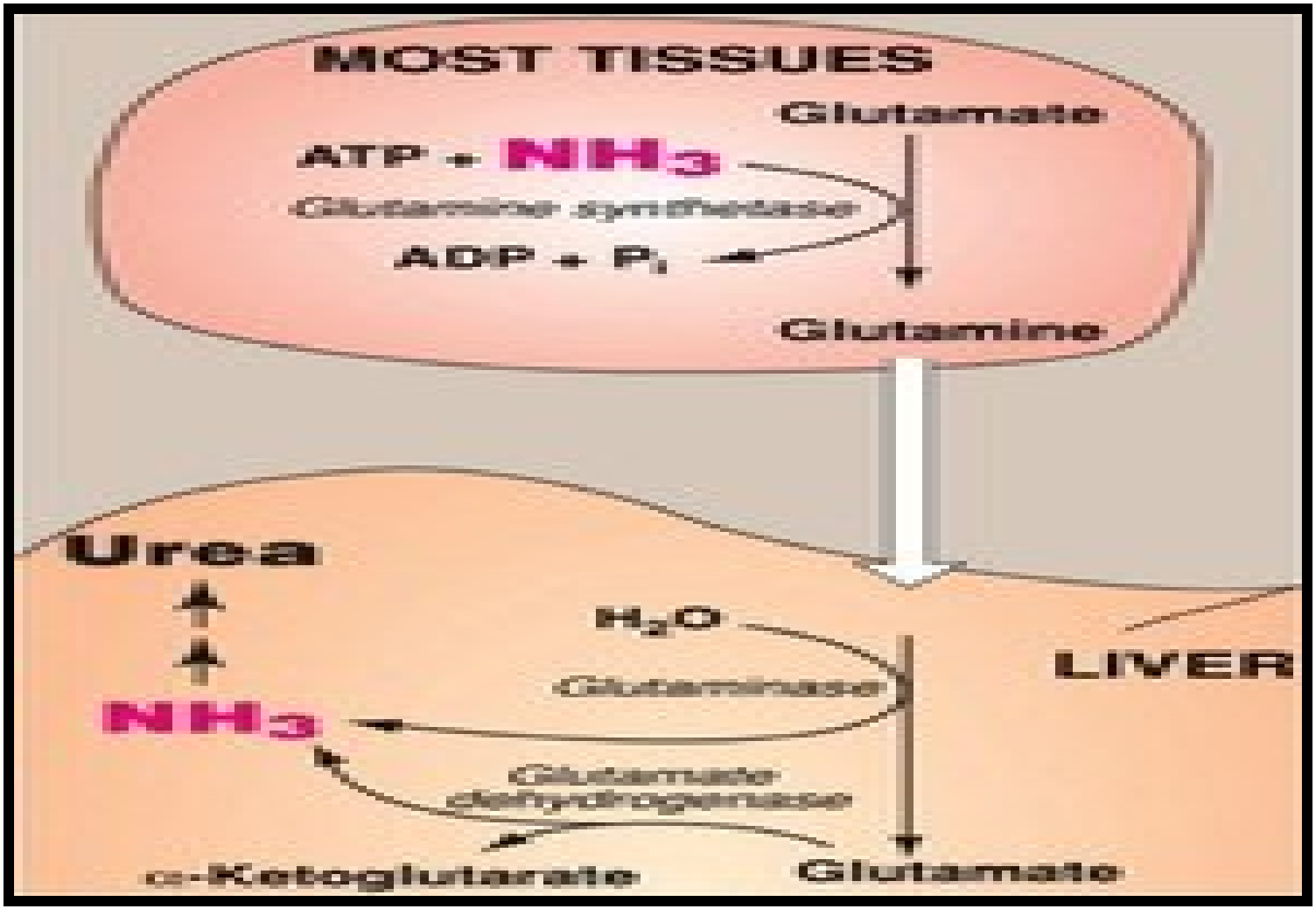
Ammonia Transport

1) Ammonium ion (NH4+)

2) Ammonia Transport in the form of glutamine

- Glutamine synthetase (mitochondrial enzyme) fixes ammonia as glutamine.





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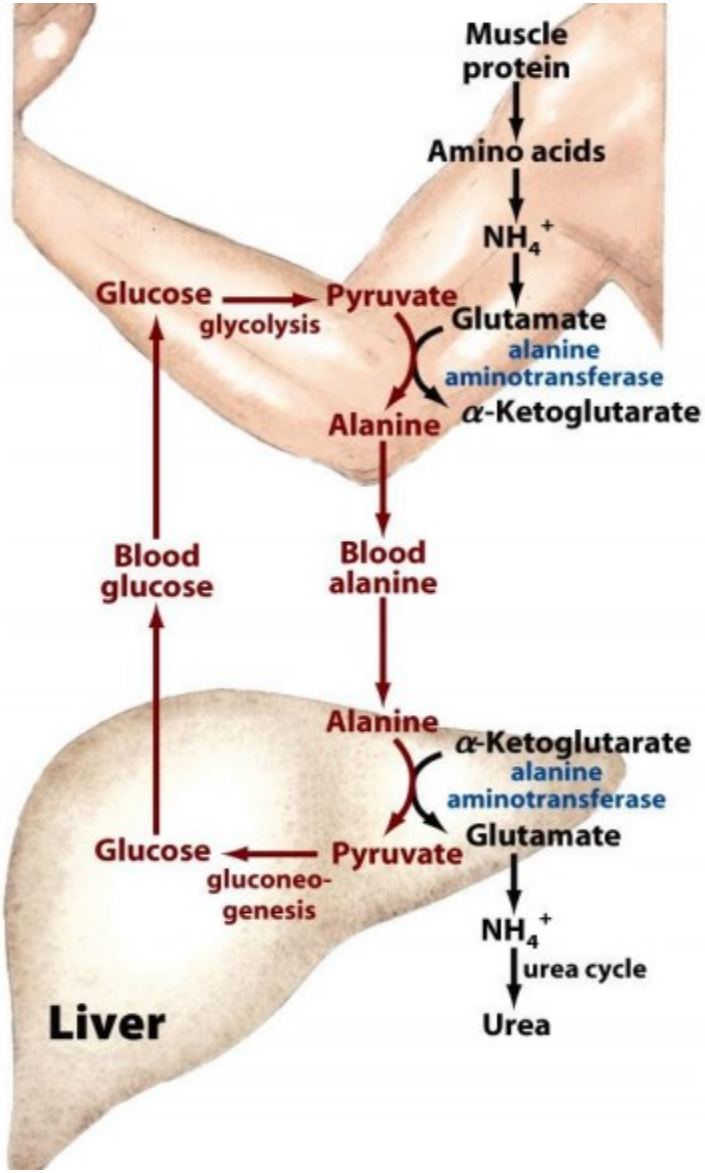
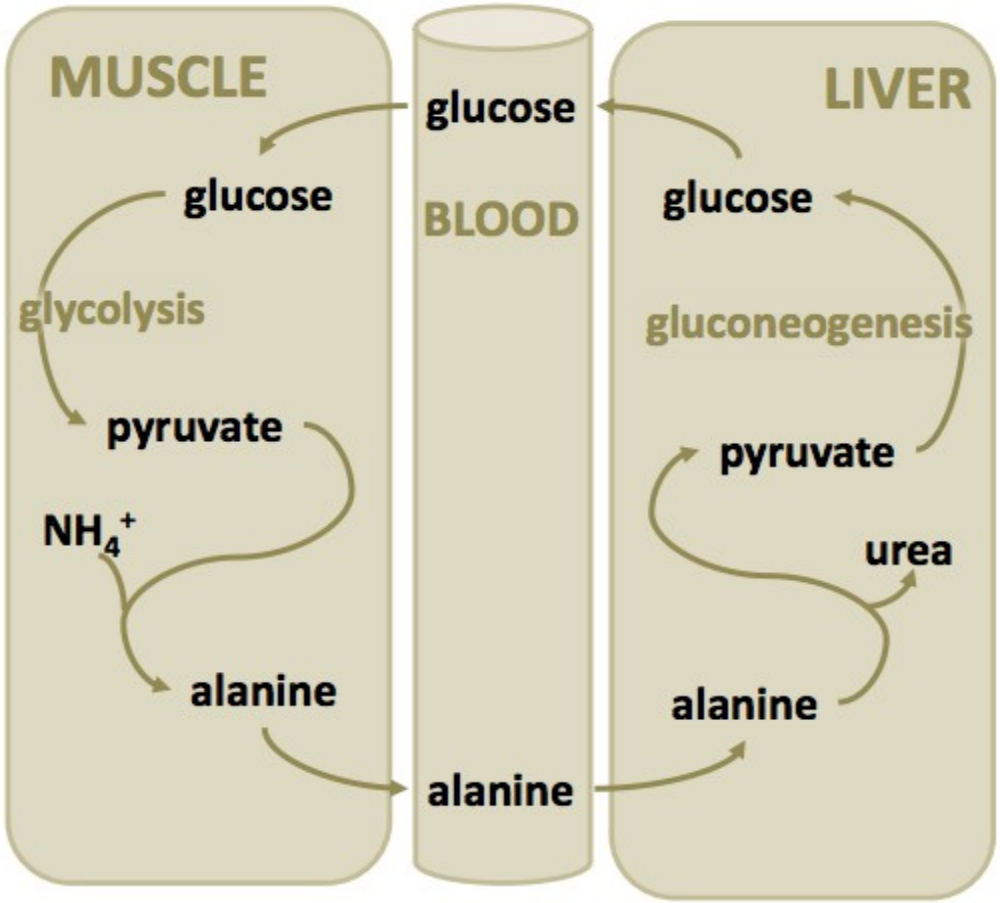
3) Ammonia Transport in the form of Alanine

Muscle sends nitrogen to the liver as alanine in addition to glutamine

Glucose Alanine cycle





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Ammonia toxicity, transport and detoxification through urea cycle (Quiz)

Ammonia is toxic to the brain. Justify

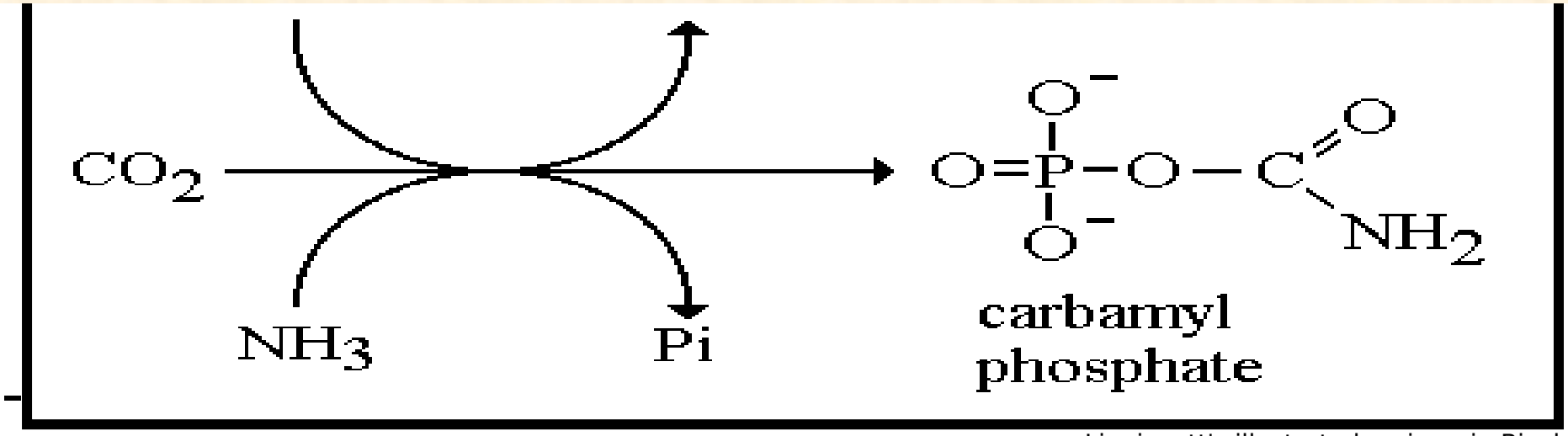
Urea cycle

-Synthesis of urea occurs in the liver in 5 reactions.

-The first 2 reactions proceed in mitochondria of liver cells.

-while the remaining 3 proceed in cytosol of liver cells.

1) Biosynthesis of carbamoyl phosphate



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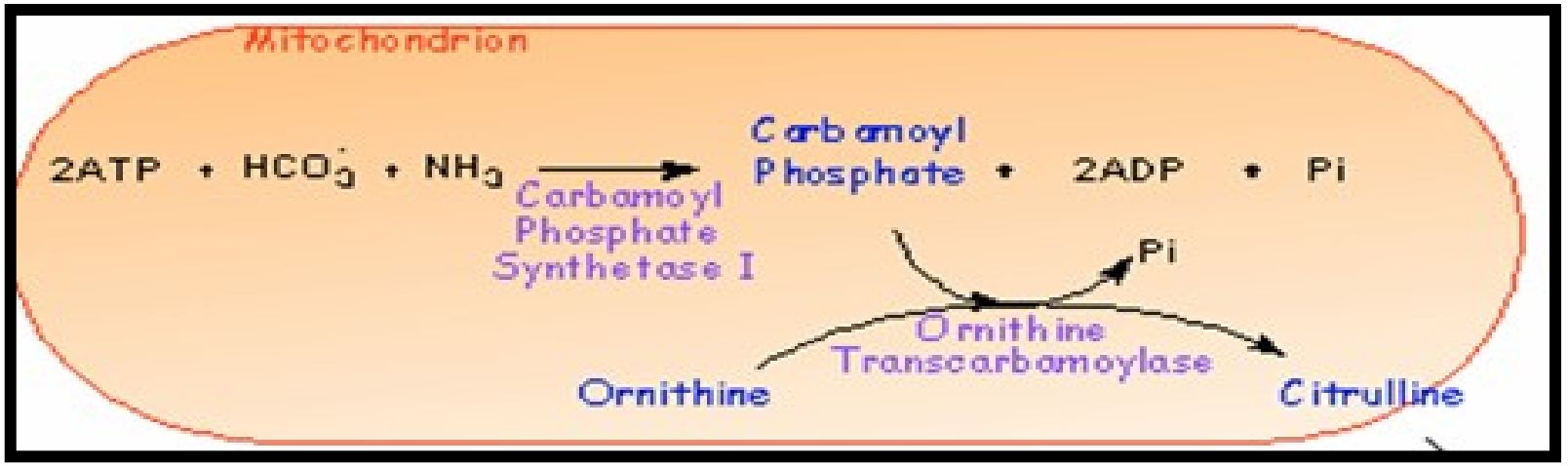
energy
(CO2 is a product of citric acid cycle, ammonia is derived from glutamate by deamination, the phosphate and energy are derived from ATP).
- It is catalyzed by mitochondrial carbamoyl phosphate synthetase I (CPS I) (the rate-limiting enzyme of urea cycle).
- 2 ATPs are required

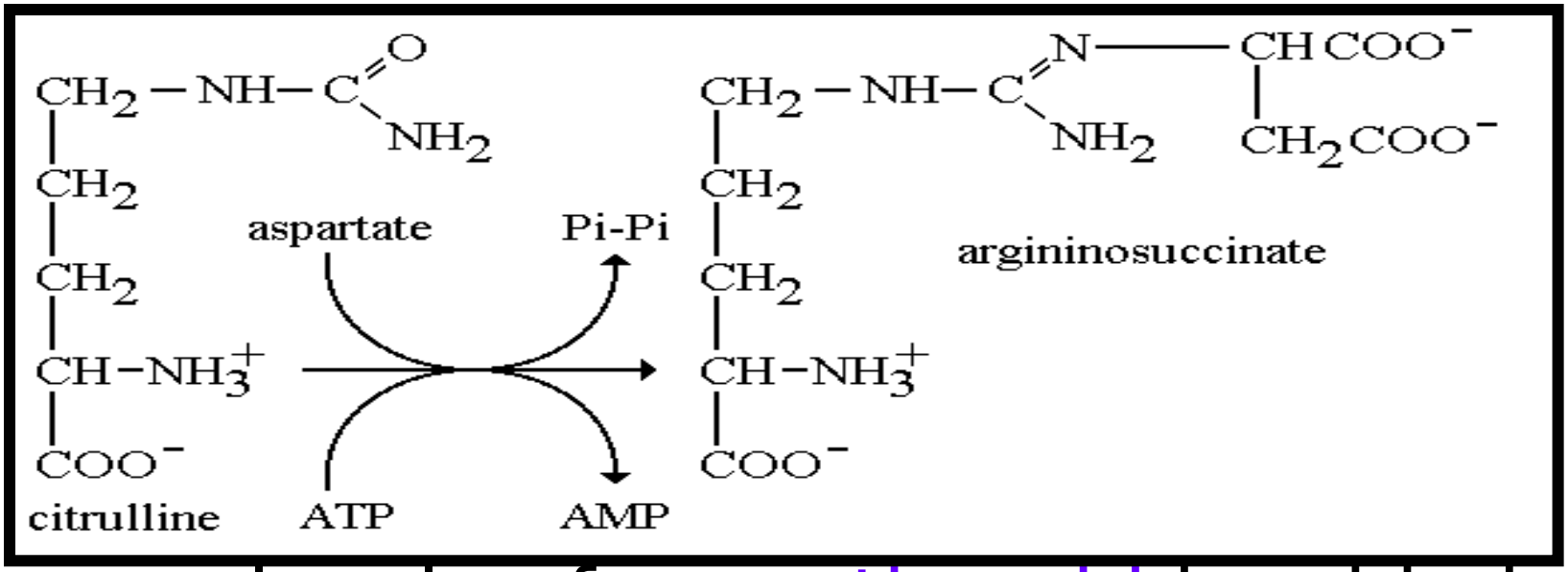
2- Formation of citrulline



https://www.google.com/search?q=ornithine+transcarbamylase&hl=en-US&source=lnms&tbm=isch&sa=X&ved=0ahUKEwioqreJyonkAhVDDewKHfArDP4Q_AUIESgB

The carbamoyl portion of carbamoyl phosphate is transferred to ornithine by ornithine transcarbamoylase (OTC) and the high-energy phosphate is released as inorganic phosphate. The reaction product, citrulline, is transported to the cytosol.

3- Formation of argininosuccinate



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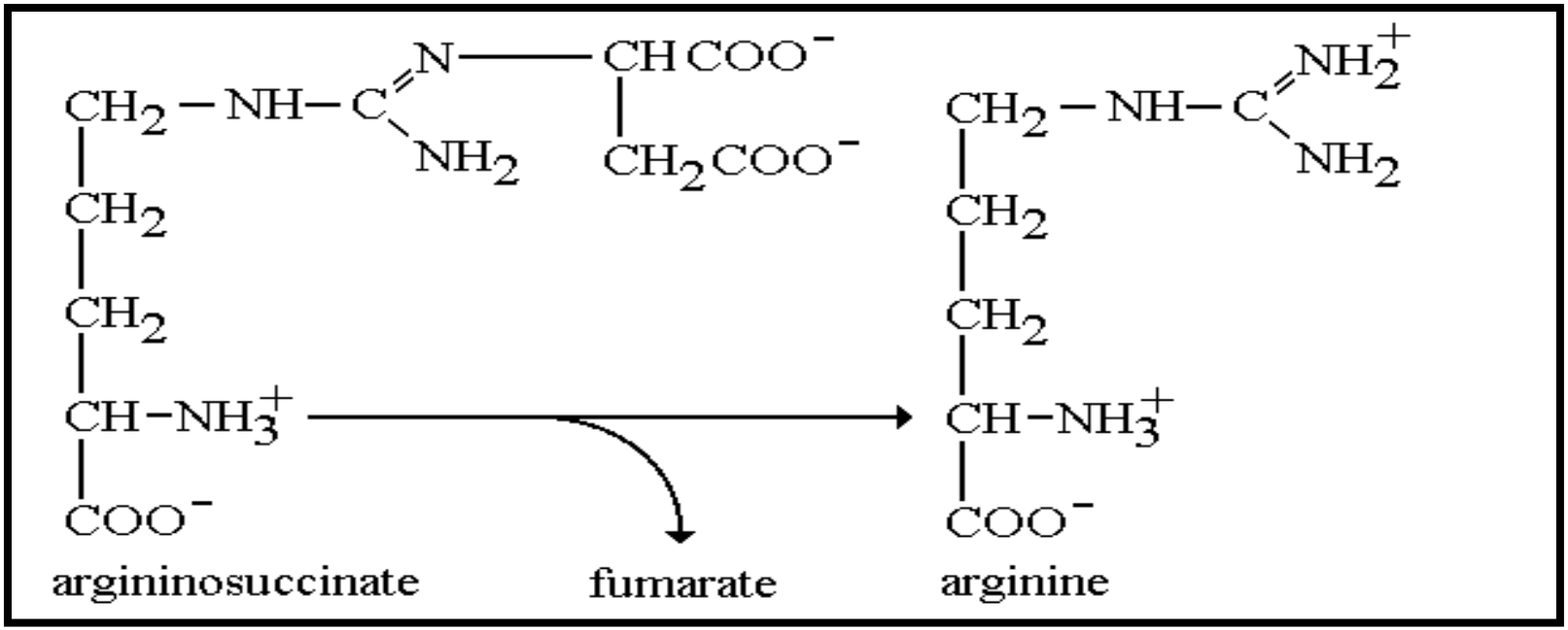
- One molecule of aspartic acid is added to citrulline forming argininosuccinate which provides the 2nd N of urea.
- Catalyzed by argininosuccinate synthetase

4- Cleavage of argininosuccinate



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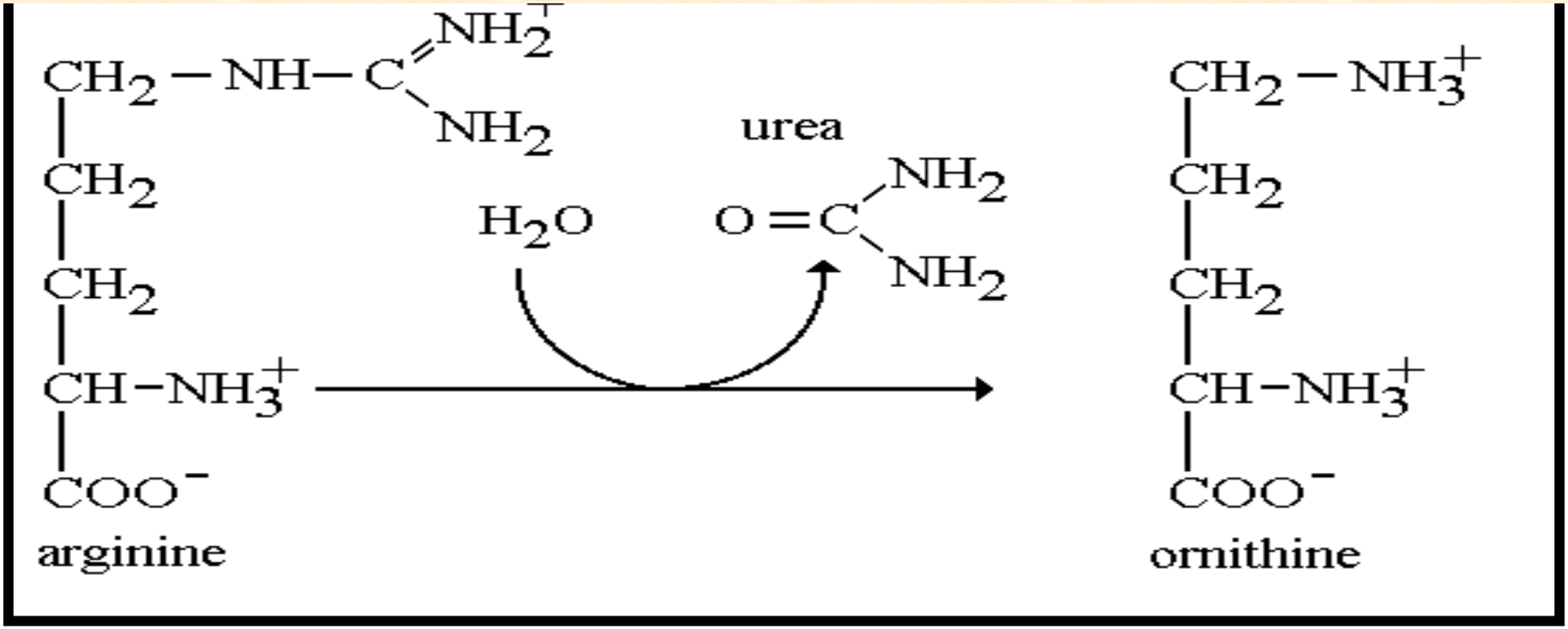
Argininosuccinate is cleaved by argininosuccinate lyase to yield arginine and fumarate

5- Cleavage of arginine by arginase into urea and ornithine



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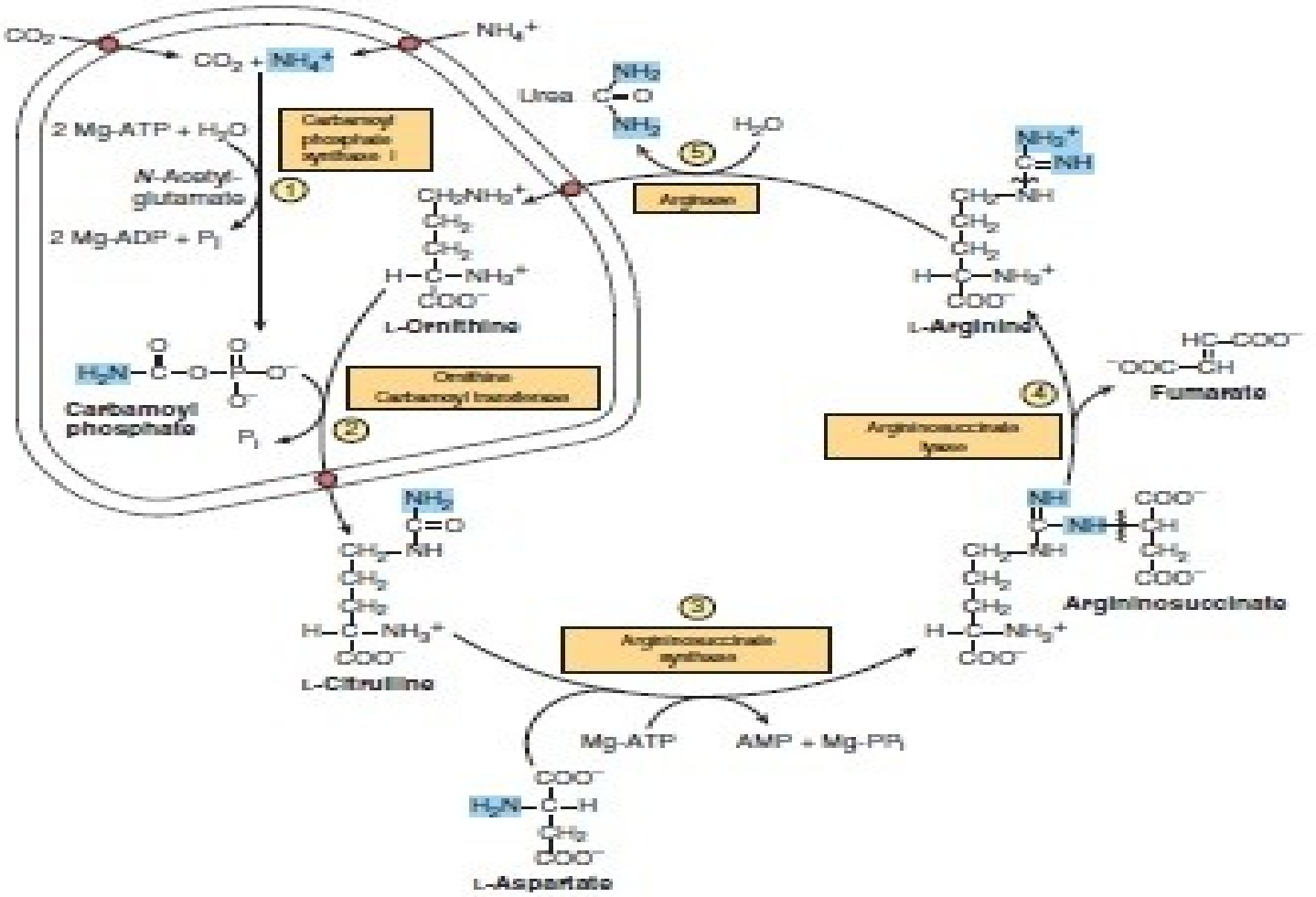
N.B Ornithine and citrulline are basic amino acids that participate in the urea cycle, moving across the inner mitochondrial membrane via a cotransporter.

Urea cycle



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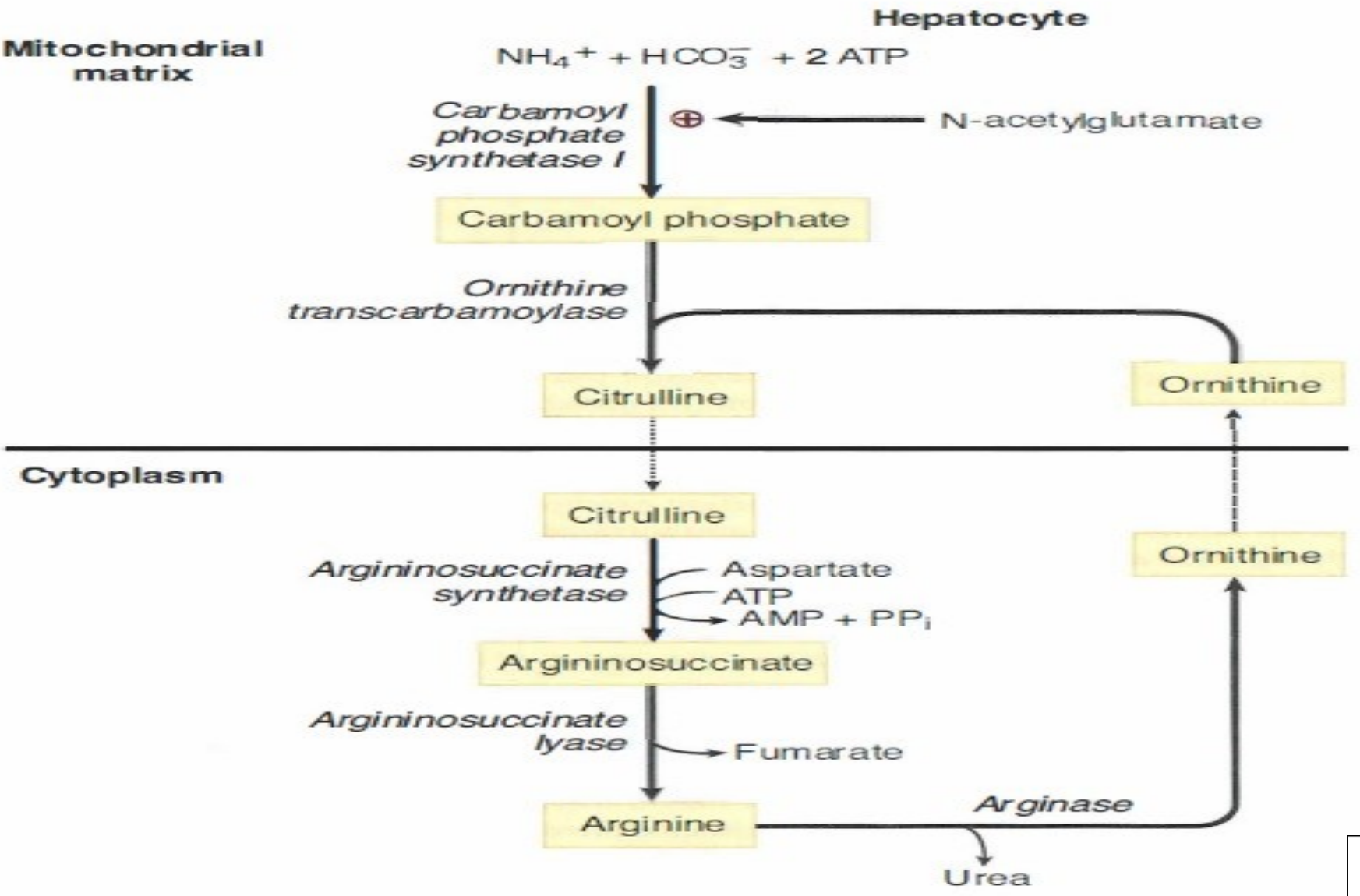
Urea cycle



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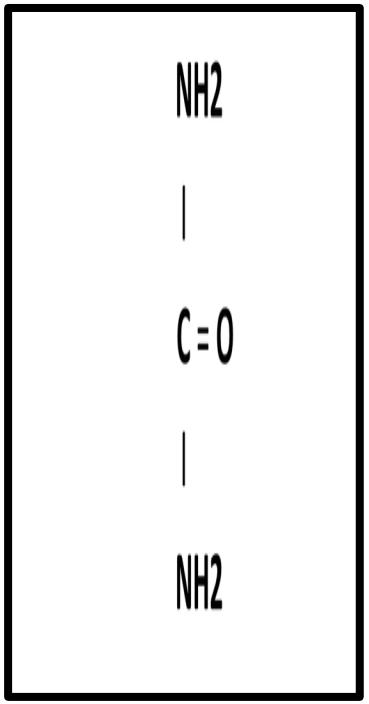
Sources of urea nitrogen

Urea contains 2 nitrogen atoms:



1) The first arises from ammonia.

2) The second arises in cytosol from aspartate

Source of carbon

CO_2

Urea Formation:

Although the urea formation requires the participation of 3 ATP molecules, yet it consumes 4 ATP from the energetic point of view as 4 high energy phosphate bonds are hydrolyzed" recall that conversion of ATP to AMP release PPi".

Lecture Quiz

In patients with liver cell failure, the following is NOT elevated in blood:

(A) Ammonia
(B) Glutamine
(C) Alanine
(D) Urea

Summary

- Hyperammonemia, has toxic effects in the brain (cerebral edema, convulsions, coma, and death).
- Most excess nitrogen is converted to urea in the liver and goes through the blood to the kidney, where it is eliminated in urine.

SUGGESTED TEXTBOOKS

- Lippincott's illustrated reviews in Biochemistry by P.C. Champe, R.A. Harvey and D.R. Ferrier
- Fundamentals of Clinical Chemistry (Tietz)
- "Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin
- "Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell

THANK YOU